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Maropitant but not ondansetron inhibits tranexamic acid-evoked emesis. A controlled blinded randomized crossover trial

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Curriculum vitae

Vetsuisse Faculty University of Zürich (2019)

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Maropitant, aber nicht Ondansetron hemmt die durch Tranexamsäure verursachte Emesis. Eine kontrollierte verblindete randomisierte Crossover-Studie

Ziel dieser Studie war es, die Häufigkeit von Tranexamsäure (TXA) -induzierter Übelkeit und Erbrechen nach prophylaktischer Anwendung von zwei Antiemetika, Ondansetron und Maropitant, im Vergleich zu einer Kontrollkochsalzlösung zu bewerten. In dieser prospektiven, randomisierten Vergleichsstudie wurden acht erwachsene, zu Versuchszwecken gezüchtete Beagles einer Behandlung ausgesetzt. Hunde erhielten dreimal jeweils drei Behandlungen nach einer Auswaschphase. Entweder Maropitant 1 mg/kg, Ondansetron 0,2 mg/kg oder Salzlösung wurde intravenös (IV) gegeben und zehn Minuten später TXA 50 mg/kg IV. Der Schweregrad der Übelkeit wurde mit einer visuellen Analogskala (VAS) bewertet. Die statistische Signifikanz wurde auf $p<0,05$ festgelegt.
Insgesamt haben 5 von 8 Hunden (62,5%) erbrochen, jedoch keiner nach Maropitant. Es gab eine signifikante Reduktion in der Häufigkeit von Erbrechen nach Maropitant ($p<0,0001$), nicht jedoch nach Ondansetron oder Kochsalzlösung ($p=0,53$). Die höchsten Übelkeits-VAS erschienen in den ersten 5 Minuten. Die Wirkung von Maropitant und Ondansetron gegen Kochsalzlösung auf den Schweregrad der Übelkeit war statistisch nicht signifikant ($p=0,069$). Somit verhinderte Maropitant wirksam das Erbrechen im Vergleich zu Ondansetron und Placebo.

Erbrechen, Übelkeit, Antifibrinolytika, Nebenwirkungen, Hunde

Vetsuisse Faculty University of Zürich (2019)

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Maropitant but not ondansetron inhibits tranexamic acid-evoked emesis. A controlled blinded randomized crossover trial

The aim of this study was to evaluate the incidence of tranexamic acid (TXA)-induced nausea and vomiting after the prophylactic use of two antiemetics, ondansetron, and maropitant, compared to saline. This was prospective, blinded, placebo-controlled, randomized, crossover study. Eight adult, purpose-bred, Beagle dogs were exposed to treatment. Dogs received three treatments on three occasions with a 3-week washout period. Either maropitant (1 mg/kg), ondansetron (0.2 mg/kg) or saline solution was given intravenously (IV), followed 10 minutes later by 50 mg/kg IV TXA. The severity of nausea was assessed by the blind observer for 30 minutes with a visual analog scale (VAS). Statistical significance was set at $p<0.05$.
None of the dogs vomited after maropitant. Emesis occurred in 5 out of 8 dogs (62.5%). There was a significant effect on vomiting of maropitant against saline ($p<0.0001$) but not for ondansetron against saline ($p=0.53$). The highest nausea VAS were recorded during the first 5 minutes after TXA. The effect of maropitant and ondansetron against saline on the severity of nausea was not statistically significant ($p=0.069$).
In conclusion, the neurokinin 1 receptor antagonist maropitant, administered IV ten minutes before 50 mg/kg TXA was effective in preventing vomiting compared to ondansetron and placebo.

vomiting, nausea, antifibrinolytic agents, side effects, canine

Maropitant but not ondansetron inhibits tranexamic acid-evoked emesis. A controlled blinded randomized crossover trial

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Abstract

Objective- To evaluate the incidence of tranexamic acid (TXA)-induced nausea and vomiting after the prophylactic use of two antiemetics, ondansetron, and maropitant, compared to saline.

Design- Prospective, blinded, placebo-controlled, randomized, crossover study.

Setting- University research facility.

Animals- Eight adult, purpose-bred, Beagle dogs.

Intervention- Dogs received three treatments on three occasions with a 3-week washout period. Either maropitant (1 mg/kg), ondansetron (0.2 mg/kg) or saline solution was given intravenously (IV) in equal volumes, followed 10 minutes later by 50 mg/kg IV TXA. A blinded observer evaluated the dogs for signs of vomiting and nausea for 30 minutes. The severity of nausea was assessed with a visual analog scale (VAS) and recorded at baseline prior TXA, and at the end of three observational periods: 0-5, 5-15, 15-30 minutes after TXA. A generalized linear mixed effect model was used to assess for group and period effects. Statistical significance was set at $p < 0.05$.

Measurements and Main Results- None of the dogs vomited after maropitant. Emesis occurred in 5 out of 8 dogs (62.5%), a median (range) of one time (1 – 2) after ondansetron and one time (1-3) after saline. There was a significant effect on vomiting of maropitant against saline ($p<0.0001$) but not for ondansetron against saline ($p=0.53$). The highest nausea VAS were recorded during the first 5 minutes after TXA with a significant reduction of VAS variability in the maropitant group ($p=0.003$). The effect of maropitant and ondansetron against saline on the severity of nausea was not statistically significant ($p=0.069$).

Conclusion- The neurokinin 1 receptor antagonist maropitant at the dose used, administered IV ten minutes before 50 mg/kg TXA was effective in preventing vomiting compared to ondansetron and placebo. Our results support the prophylactic IV administration of maropitant in dogs that are scheduled to receive TXA.

Keywords: vomiting, nausea, antifibrinolytic agents, side effects, canine

Abbreviations

IV intravenous

TXA tranexamic acid

VAS visual analog scale

Introduction

Tranexamic acid (TXA) is an antifibrinolytic drug, which reversibly adheres to the lysine-binding site on plasminogen and inhibits its activation into plasmin. In consequence, TXA results in suppression of fibrinolysis and stabilization of the clot.[1] *A* large body of scientific evidence from human medicine has been published showing that TXA reduces blood loss and decreases blood transfusions requirements.[2-5] Veterinarians have gained interest in antifibrinolytic drugs and multiple studies supporting their use in dogs have been published. To date, TXA has been shown effective as an antifibrinolytic drug in dogs infected with Angiostrongylus vasorum as well as in Greyhounds undergoing ovariohysterectomy and limb amputations. [6-8] Moreover, antifibrinolytic drugs such as TXA, have the potential to reduce blood loss in dogs with spontaneous hemoperitoneum, as hyperfibrinolysis has been found to be an important cause of hemorrhage in these circumstances.[9]

In people and dogs, intravenous (IV) administration of TXA is well known to induce nausea and vomiting.[10,11] Nausea is a very unpleasant experience affecting the comfort of the patient. Analysis of a questionnaire for pet owners about perioperative nausea has shown agreement for additional financial contribution to decrease the occurrence of nausea in their pets.[a] Although vomiting in healthy patients may be harmless, in critically ill patients it can lead to a marked increase in morbidity and mortality due to major complications, such as aspiration pneumonia, esophagitis, and esophageal stricture.[12-14] Additionally, in patients with head trauma, vomiting raises the intracranial pressure, which can lead to further deterioration of the neurologic status.[15]

Various and potent antiemetics are available in dogs, working at different parts of the emetogenic pathway. Maropitant, a neurokinin 1 receptor antagonist, has been effective against multiple centrally and peripherally acting emetics as well as against clinical causes of vomiting.[16]

Ondansetron as a 5-hydroxytryptamine (serotonin) 3 receptor antagonist is used as the first line treatment of drug-induced emesis, especially in chemotherapy patients and in the prophylaxis of postoperative nausea and vomiting.[17] Aprepitant, a neurokinin 1 receptor antagonist, used in human medicine, was able to decrease kaolin intake in rats previously exposed to TXA, while ondansetron and domperidone (a dopamine 2 receptor antagonist) failed to do so.[18] Rats are a non-emetic species and pica behaviors are assessed as indicators of nausea in preclinical studies. However, some doubt arose whether results of preclinical studies assessing potential emetogenic substances in rats with pica behaviors can directly be translated to the emetic effect of these substances in other species.[19]

The goal of the present study was to evaluate the effectiveness of prophylactic maropitant and ondansetron in preventing TXA-induced vomiting in a blinded placebo-controlled crossover study in Beagle dogs. The secondary aim was the evaluation of the effects of both treatments on nausea after TXA. The study hypothesis was that maropitant would be able to suppress TXA evoked emesis while ondansetron and placebo would not affect it.

Material and methods

This project has been approved by the xx Ethics Committee on Animal Research of the xx (authorization number xx).

Animals

Eight healthy, purpose-bred, Beagle dogs (4 intact females, 4 intact males), aged 6.5 (6-6.5) years old (median (range)), and weighing 13.1 kg (10.7-16.6 kg) were included in the study. Dogs were considered healthy based on physical examination and basic blood work (packed cell

volume, total plasma protein, and venous blood gas analysis).[b] Dogs were permanently housed in an approved facility, four same-sex individuals per cage, with free access to outside fenced area, unlimited access to water and commercial diet[c] provided once a day at 12:00. Since the experimental procedures were performed in the morning, all dogs received 100 g of soft dog food[d] approximately 20 minutes before the start of the study. The research was conducted at the dogs' usual residence by the experimental facility, in a dedicated room well known to the animals. Dogs were moved one at the time to the experimental room and returned to their conventional cages once the study was concluded. A week before the study inauguration, dogs were familiarized with the study investigators and habituated to the experimental design. This time also allowed the investigators to familiarize with the animals individual behavior.

Randomization

This study was performed as a randomized, prospective, crossover, blinded, placebo-controlled trial. Block randomization with balanced permutations was performed using an online-based software.[e]

Treatments

Animals were allocated to receive one of three possible treatments on the single occasion, with a three-week washout period between treatments. Either 1 mg/kg of maropitant[f] 0.2 mg/kg ondansetron[g] or 3 ml saline (0.9% sodium chloride)[h] was administered IV on each occasion through an aseptically placed 22-Ga x 2.5 cm cephalic vein catheter.[i] All medications were equalized to a total volume of 3 ml with 0.9 % sodium chloride (if needed) and administered over 2 minutes. Ten minutes later all animals received 50 mg/kg TXA[j] IV over 2 minutes.

Study outcomes

One blinded study investigator (MK) was responsible for all assessments of the dogs for 30 minutes. The primary study outcome was the occurrence of vomiting. Additionally, the number of episodes and the time of their occurrence were documented. Vomiting was defined as the expulsion of gastrointestinal content through the mouth, accompanied by forceful, and sustained abdominal muscle contractions. The secondary study outcome was the severity of nausea assessed by means of a Visual Analog Scale (VAS)[20] at four-time points: baseline prior to administration of TXA, and during the defined time periods 0-5, 5-15 and 15-30 minutes after TXA. The VAS score was made by placing a mark on a 100mm line at the end of each observational period. More intense nausea received higher marks (0-100 mm). Signs interpreted as nausea included: lip and nose licking, increased frequency of swallowing, ptyalism, gulping, panting, restlessness, whining and winking.

Sample size calculations

The assumptions were 100% incidence of vomiting (without antiemetic) according to former study in Beagle dogs using the same dose regime of TXA.[11] Results of a priori power analysis indicated that eight dogs would be sufficient to detect a reduction of vomiting from 100% in untreated to 10% in treated dogs with a power of 80% and a type one error of 5 %.

Statistical analysis

To assess the group effect (maropitant/ondansetron/saline) and the period effect (A/B/C) on vomiting (YES or NO) and on VAS (mm), a generalized linear mixed effect model (binomial) was used. The period effect was assessed by the Wald Test. All analyses were performed with the software package R version 3.3.3[k] and the package geepack.[21] Graphs were created with graphpad.[l] Statistical significance was set at $p < 0.05$.

Results

Vomiting episodes

None of the eight dogs receiving maropitant vomited, while after ondansetron and saline treatments five out of eight dogs vomited (3 males, 2 females) (62.5% occurrence). There was a significant effect of maropitant against saline ($p<0.0001$) but not for ondansetron against saline ($p=0.53$). There was no evidence of a period effect ($p=0.14$). The frequency of vomiting is presented in Figure 1. The first emetic episode after the end of TXA administration occurred within 55 (33-90) seconds (median (range)) for ondansetron and within 76 (31- 192) seconds after saline.

Severity of nausea

The highest nausea VAS were recorded during the first five minutes after TXA (Figure 2). One female dog that never vomited displayed a VAS of 6 mm after saline pretreatment in the first five minutes after TXA administration and no nausea at all during the other two exposures. The effect of maropitant and ondansetron against saline was not statistically significant ($p = 0.069$). However, in the maropitant group a significant reduction of VAS variability could be detected ($p=0.003$). A significant period effect could be observed ($p<0.0001$).

Discussion

Maropitant administered IV ten minutes in advance abolished TXA-induced vomiting in dogs. Ondansetron did not reduce the incidence of vomiting compared to saline. The dogs that received maropitant still displayed signs of nausea with a lower variability in VAS scores than with the other treatments. Overall, the severity of nausea as assessed by VAS was considered mild

to moderate across all the treatments. Emetic episodes were short, fast in onset and occurred up to three times, all within the first four minutes after the end of TXA administration.

The neurokinin 1 receptor-mediated pathway has been hypothesized as the potential mechanism behind TXA-evoked emesis in rats, in which pica behaviors were assessed.[18] Kaolin intake, a marker of pica behaviors, is a model for nausea in rats. In the mentioned study, kaolin intake was decreased by concomitant administration of TXA and aprepitant, whereas no difference was found for ondansetron and domperidone. Additionally, immunohistochemical staining of the brain after TXA alone and after TXA with aprepitant, has found that TXA with aprepitant decreased the neuronal activity in both the area postrema (chemoreceptor trigger zone) and the nucleus tractus solitarius (vomiting center).[18] Our results in dogs corroborate the findings of Kakiuchi in rats,[18] and likely a neurokinin 1 receptor pathway is involved in nausea and vomiting side effects of TXA. Involvement of a serotonin pathway seems less likely but cannot be excluded, despite the fact that the potent serotonin receptor antagonist ondansetron did not affect nausea and vomiting in our study. It is important to mention that we chose a one standard dose of ondansetron (0.2 mg/kg) due to the clinical nature of our research.[22] In a low dose cisplatin model of nausea and vomiting in dogs, ondansetron, at the dose of 0.5 mg/kg IV, was as effective as maropitant in suppressing emesis and highly more effective in suppressing nausea (90% vs. 25% AUC reduction).[17] It is possible that higher doses of ondansetron may have produced greater anti-emetic and anti-nausea effects. Perhaps more time would have been necessary for ondansetron to distribute to receptor sites within the brain or peripheral sites of action to counteract the rapid action of TXA. On the contrary, in the study of Santos et al. in cats, waiting for 30 minutes after 0.22 mg/kg intramuscular ondansetron injection did not diminish vomiting after

dexmedetomidine.[23] If ondansetron would require more time to be effective against the TXA in our study, this would render the drug less practical in a clinical situation. TXA is most frequently used in emergency situations and a time delay for ondansetron to prevent emesis could be detrimental.

In a study assessing the vomiting effects of TXA,[11]a single TXA bolus of 50 mg/kg has been shown to induce vomiting in all ten Beagle dogs. In the same study, reduced dose rates caused a lower incidence of vomiting, and it was hypothesized that a dose dependency exists, though vomiting with dosages as low as 15 mg/kg has also been reported.[24] Most recently, the dose of 50 mg/kg TXA was further investigated in 137 dogs, in which the incidence of vomiting was 84.7%. [25] In our study, the administration of 50 mg/kg TXA over 2 minutes resulted in an incidence of vomiting of only 62.5%. These findings suggest that either we injected the TXA slower than in the previous studies leading to lower peak plasma concentrations of TXA, or individual differences in sensitivity to the vomiting side effects of TXA exist. The differentiation between these two reasons, however, cannot be answered by the current study.

In veterinary medicine, further work is needed to establish required plasma levels as well as intravenous dosing regimes of TXA. In an *in vitro* study TXA plasma levels required to inhibit tissue plasminogen-induced hyperfibrinolysis in dogs were assessed. [26] The calculated IV dose of TXA to reach the required plasma levels for dogs were as high as 150 mg/kg. In another study, where TXA was used to inhibit hyperfibrinolysis in Angiostrongylus vasorum infected patients, some dogs required cumulative doses of up to 80 mg/kg TXA IV, to stop bleeding.[8] Whether maropitant is also effective in preventing TXA induced vomiting at dosages beyond 50 mg/kg remains to be determined and was beyond the scope of the present study. In dogs, recent

pharmacokinetic data showed that a bolus of 20mg/kg TXA IV reaches plasma concentrations that are higher than the ones necessary to inhibit fibrinolysis. [m]

Interestingly, the dogs receiving maropitant still displayed signs of nausea. It is a well-known phenomenon in humans undergoing chemotherapy that the occurrence of nausea may persist despite the inhibition of emesis with antiemetic drugs.[27] After all, nausea seems to be a more complicated phenomenon involving still undetermined neurotransmitters and mechanisms, which until date, are not fully understood.[27] Another explanation for persistent nausea could be the short interval between the administration of maropitant and TXA. When in one study maropitant was administered subcutaneously, incomplete absorption and thus incomplete effect at the time of assessment has been hypothesized.[28] Nevertheless, in our study maropitant has been administered IV and therefore effective plasma levels should have been reached imminently according to pharmacokinetic data.[17] It is likely that the time interval of ten minutes between maropitant and TXA administration could be further shortened. Yet, this study was not designed to answer that question.

In humans, female patients are reported to be more prone to develop postoperative nausea and vomiting. The reason for this is unknown.[29] In our study, of the three dogs that did not vomit, one was male and two were females. One of the two females that did not vomit displayed only minimal (6 mm on VAS scale) signs of nausea after TXA. In veterinary medicine, there are no data available about the prevalence of nausea and patient-specific risk factors (sex, breed, size, type of surgery, medications).

Our study has some limitations. Overall, we report a lower incidence of vomiting than announced elsewhere.[11] The effects of maropitant on induction of vomiting could therefore only

be tested in five out of eight dogs. However, maropitant was effective in suppressing emesis and reducing the variability in severity of nausea when compared to ondansetron and saline treatment. Although crossover designs allow to decrease the number of required animals because inter-individual differences are eliminated, the period effect found in this study is a common problem. The small sample size of eight dogs led to an imbalanced group allocation per period (Figure 2) and made it impossible to disentangle the effect of period and group on VAS. Additional individual effects like familiarization of the dogs to the experimental model or systematic intra-observer differences in VAS allocation between the three observation periods can occur. Screening for nausea remains difficult, and only subjective measures are possible in veterinary medicine. In this study, a Visual Analog Scale was used as a severity scale for nausea. Though VAS is the most commonly used tool across research about emesis, its subjective nature can lead to misdiagnosis, over- or underestimations.[27] In the current study consistently the same, blinded observer assessed all dogs after all treatments to exclude inter-observer variability. No validated method for nausea assessment is available in veterinary medicine at the moment. A recent study identified blood biomarkers such as cortisol and arginine vasopressin as an objective method for nausea screening in a low-dose cisplatin model.[30] The biomarkers had a weak but significant correlation with VAS score in the clinical trial performed by the same group later on.[17]

The current study supports the use of maropitant to inhibit TXA-induced vomiting in dogs. A gastrointestinal disturbance is the main side effect in human patients using TXA in their everyday life for menometrorrhagia or other coagulopathies.[10] The result of the current study supports further research using the neurokinin 1 receptor antagonist aprepitant for the treatment of TXA-induced nausea and vomiting in people.

In conclusion, the neurokinin 1 receptor antagonist maropitant administered IV at the dose used, ten minutes before 50 mg/kg TXA successfully inhibited vomiting compared to ondansetron and placebo. Our results support the prophylactic IV administration of maropitant in dogs that are scheduled to receive TXA.

Footnotes

[a] Kraus B & Cazlan C. Assessment of dog owner concern regarding perioperative nausea and vomiting and willingness to pay for anti-emetic treatment [abstract]. Presented at the American College of Veterinary Anesthesia and Analgesia Annual Meeting, Washington DC, USA; 2015.

[b] RAPIDPoint 500 Blood Gas System, Siemens, xx

[c] commercial food formula xx, Sensitive, xx, xx

[d] Hill`s a/d, Prescription Diet Canine/Feline; 156 g (5.5 oz), xx

[e] www.randomization.com, last entry 18.12.2016, 23:23:26

[f] Cerenia, Maropitant, Zoetis, xx

[g] xx, Ondansetron, xx

[h] Sodium chloride 0.9%, xx

[i] Terumo, Surflo, intravenous catheter, xx

[j] xx, Tranexamic Acid, 100mg/ml, xx

[k] R Core Team (2018). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/

[l] Graphpad Prism, Graphpad Software Inc., xx

[m] Osekavage KE, Brainard BM, Almoslem MJ et al. Pharmacokinetics of single dose IV tranexamic acid in healthy adult dogs [abstract]. Presented at the International Veterinary Emergency and Critical Care Symposium, Nashville, TN, USA; 2017

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Figure Legends

Figure 1: The frequency of vomiting per study group and with individual signs for each dog.

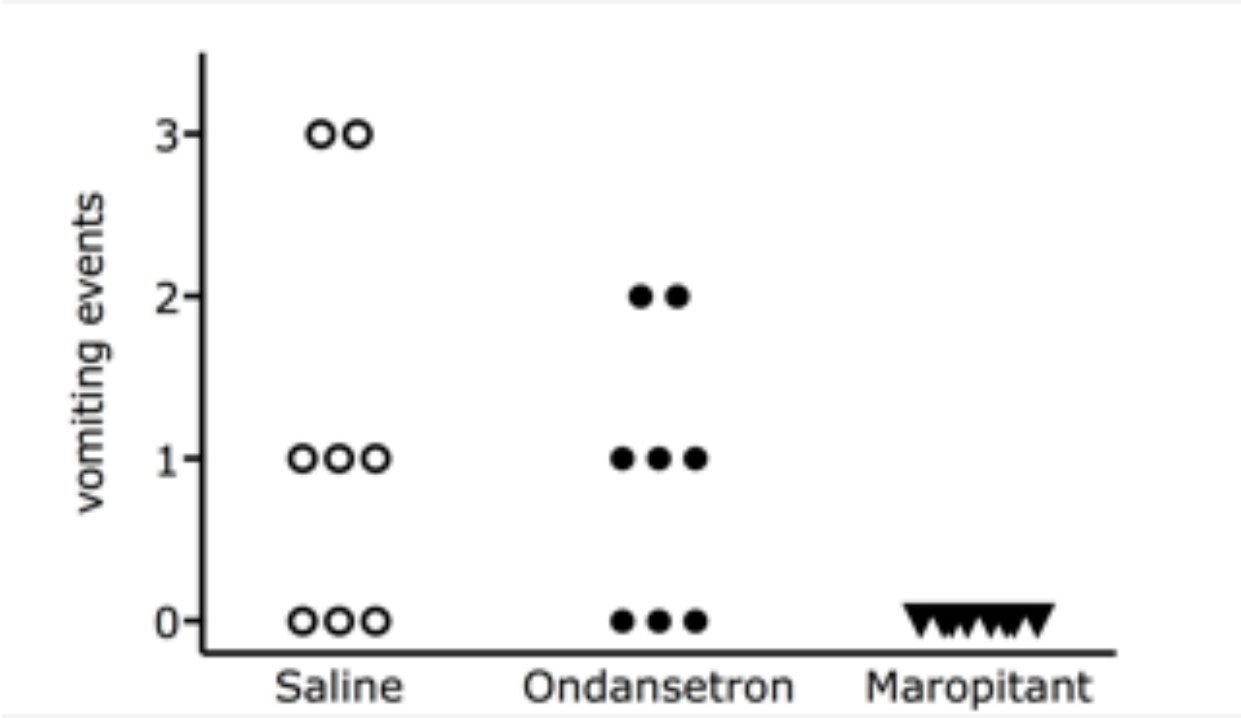
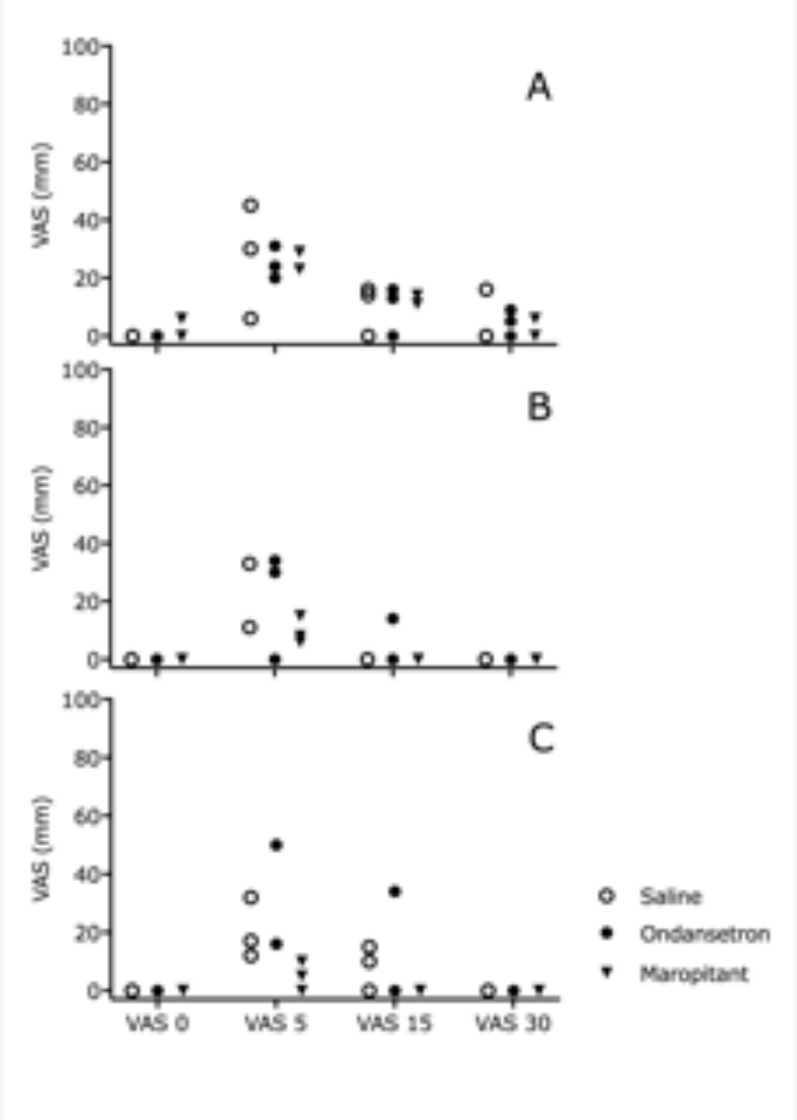


Figure 2: Visual Analog Scale in mm (VAS) for nausea at four-time points: at baseline before TXA (VAS 0), during 0 - 5 minutes (VAS 5), 5-15 minutes (VAS 15) and 15-30 minutes (VAS 30) post-TXA administration per study group. Each graph represents one period (A/B/C) with individual signs for each dog.



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